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Minocycline and the risk of acute psychiatric events in adolescence: a self-controlled case series

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ABSTRACT

Background

Minocycline has neurological anti-inflammatory properties and has been hypothesised to have antipsychotic effects.

Aim

To investigate, using routinely collected UK primary health care data, whether adolescent men and women are more or less likely to receive an urgent psychiatric referral during treatment for acne with minocycline compared with periods of non-treatment.

Method

A self-controlled case series using UK Clinical Practice Research Datalink to calculate the incidence rate ratio (IRR) of urgent psychiatric referrals for individuals, comparing periods during which minocycline was prescribed with unexposed periods, adjusted for age.

Results

We found 167 individuals who were at the time exposed to minocycline for a mean of 99 days and who received an urgent psychiatric referral. There was no difference in psychiatric referral risk during periods of exposure compared with periods of non-exposure: IRR 1st 6 weeks of exposure 1.96, 95% CI 0.82-4.71, p=0.132; IRR remaining exposure period=1.97, 95% CI 0.86-4.47, p=0.107.

Conclusions

We found no evidence in support of a protective effect of minocycline against severe psychiatric symptoms in adolescence.

Keywords: schizophrenia, acute psychiatric referral, tetracycline

INTRODUCTION

Tetracyclines, a class of broad spectrum antibiotics, have been shown to possess neurological anti-inflammatory properties (Levkovitz et al., 2007; Monte et al., 2013). There is accumulating evidence that one tetracycline, minocycline, has beneficial effects in a range of mental disorders.

Minocycline was once widely prescribed as an effective drug to treat acne (Garner et al., 2012). Case studies, small clinical trials and RCTs have reported improvements in negative and cognitive symptoms of patients with schizophrenia for whom minocycline was prescribed as an adjunctive treatment (Miyaoka et al., 2007; Miyaoka et al., 2008; Levkovitz et al., 2010; Chaudhry et al., 2012; Kelly et al., 2015). Several trials designed to test the potential use of minocycline in treatment-resistant depression are being conducted (Dean et al., 2014; Husain et al., 2015). Recently, we completed a study which examined whether the prescribing of oral minocycline for adolescents diagnosed with acne has a beneficial effect on the likelihood of later developing a psychotic illness. Using routinely collected UK health care data, no long term protective effect of minocycline on the incidence of psychiatric illness use was found (Herrero-Zazo et al., 2017).

The aim of the current study was to investigate whether or not there is a protective effect of current minocycline prescription on the occurrence of events requiring urgent psychiatric referrals. We conducted a self-controlled case series study to answer the question as to whether patients are more or less likely to receive a psychiatric referral during treatment for acne with minocycline compared with periods of non-treatment.

METHOD

Electronic health care data were provided by the UK Clinical Practice Research Datalink (CPRD), a well-established, government-owned, research database. CPRD collects and archives the anonymised medical, laboratory, referral, and prescribing records of General Practitioners (GPs). CPRD data are demographically and geographically representative of the UK population, representing around 8% of it (Herrett et al., 2010).

For this study, the source population comprised all individuals aged 15-20 with a diagnosis for acne recorded between 1991 and 2005 (*n* = 26,355).

Our study protocol was approved by the Independent Scientific Advisory Committee for MHRA database research (Independent Scientific Advisory Committee [ISAC] protocol number 15_245A2, June 2016). Studies using anonymised CPRD data for ISAC-approved observational research are covered by CPRD's broad MREC ethics approval, without the need for specific informed consent.

Study design

In this case series study, as in all case-only studies, statistical analyses were based on within-person comparisons rather than between-person comparisons: cases were matched to themselves. Individual observation periods were divided into a series of exposed and/or unexposed periods. The observation period was then further divided to take account of age. We calculated the incidence rate ratio during risk periods following initiation of minocycline relative to unexposed periods within individuals (Farrington et al., 1996). The baseline incidence rate of an individual was the Poisson incidence rate during unexposed periods, during which only the characteristics of an individual determine risk (Whitaker et al., 2006).

Study population

Individuals diagnosed with acne between 1991 and 2005, who received a prescription for minocycline, *and* an urgent psychiatric referral were included in the current analysis. The observation period was taken to start after 12 months of continuous registration with a GP, at age 15, or at the first date a patient was diagnosed with acne, whichever was latest. Observation periods were taken to end when the patient died, transferred out of CPRD, or at the last date of data collection (January 2016), whichever was earliest.

Exposure and outcome of interest

We identified all individuals with one or more recorded minocycline prescriptions of no minimum duration and any incident urgent referrals from GPs to: Child, adolescent or adult psychiatry; psychotherapy; clinical psychology; or the community psychiatric nurse. We used the CPRD classification of the urgency of the referral (urgency>=3) to ensure all minocycline users had a similar threshold for referral (or severity of symptoms). Durations of prescriptions were calculated by dividing the total recorded quantity received by the numeric daily dose. To account for missing information regarding dose and duration of treatment, the median obtained from all other minocycline prescriptions was imputed. In the main analysis, patients with prescriptions for isotretinoin and doxycycline were excluded. (Isotretinoin has been independently associated with severe mental illness and doxycycline has very similar properties to minocycline.)

Risk windows self-controlled case series

The observation time of patients was divided into the following risk windows: 1) 0 to 42 days after prescription of minocycline, 2) the remaining minocycline exposed time, and 3) a 2-

month post-exposure period representing a shift from full exposure to an entirely unexposed state; the "baseline" period comprised all remaining unexposed time (see Figure 1). The first risk window, 42 days, is in line with the recommended minimum duration of treatment with minocycline for the treatment of acne. A grace window of 14 days between two prescriptions was created to allow for late repeat prescriptions and prescription patterns falling within this window were analysed as continuous exposure. Age was modelled explicitly in one-year age bands, except ages 38-44, which were prospectively grouped together owing to anticipated small numbers. Subgroup analyses were performed for men and women. Incidence rate ratios (IRR) and confidence intervals (CI) were calculated using conditional Poisson regression. Each subject contributed a likelihood of a referral event occurring in a particular age and exposure group. The overall likelihood was calculated by summing over all individual log-likelihoods.

Sensitivity analyses

Five sensitivity analyses were conducted post-hoc:

1. In order to further improve sensitivity of the age effect, we ran a model in which individuals who experienced the event of interest, but who were not exposed to minocycline, were added. All these cases contributed to the baseline period, which encompassed all unexposed time. Their observation periods for these individuals were divided in risk windows solely determined by age.
2. A sensitivity analysis was conducted in which the main outcome was changed from urgent psychiatric referrals to psychotic symptoms. For this analysis the incident recordings of the following symptoms/diagnoses were included: hallucinations, delusions, psychotic symptoms or psychosis.
3. The exposure of interest was extended to include users of minocycline and/or doxycycline.

4. The first two days after receipt of a prescription for minocycline and the remaining exposure periods were analysed separately to allow for an estimation of a possible increase in diagnoses at the point of GP contact. That is, the act of seeing a GP when receiving a prescription for minocycline might be associated with an increased likelihood of diagnosis of severe mental health disorders.
5. *All* psychiatric referrals were used as an outcome measure, rather than *urgent* referrals to allow for an outcome measure with greater sensitivity.

RESULTS:

Main analysis

Our main outcome of interest – urgent psychiatric referral – comprised a mixture of symptoms ranging from acute anxiety to hallucinations. Most referrals (43.1%) were for depression, low mood and/or anxiety. Data rating the urgency of referral were not entered for most individuals (57.56%).

In total, 219 individuals met the inclusion criteria and received both a prescription for minocycline and an urgent psychiatric referral during their observation period: 42 of these were excluded because of doxycycline use and 10 because of isotretinoin use. Of the remaining 167 individuals, 90 (54%) were men (see Table 1). The mean age of individuals at the start of the observation period was 15.98 years (Standard Deviation [SD] 1.46). The average age of individuals at the end of the observation period was 27.7 years (SD 6.19). On average, a single exposure period lasted 99 days (14 weeks). The average age at which patients in the study population received their first psychiatric referral was 23.1 years (SD=5.47).

Overall, 153 individuals received a referral during a period of non-exposure (incidence rate=764.32 psychiatric referrals per 10,000 patient years [py]), compared with 6 in the first 6 weeks of minocycline exposure (1572.88 per 10,000 py) and 8 in the remaining exposure period (1671.91 per 10,000 py). No events were recorded in the 2 months post-exposure period.

The age-adjusted incidence rate ratio (IRR) suggested there was no difference in psychiatric referral risk between exposed and non-exposed periods (1st 6 weeks of exposure: IRR 1.96, 95% CI 0.82-4.71, p= 0.132; remaining exposure period: IRR 1.97, 95% CI 0.86-4.47, p= 0.107, see Table 2). There was weak evidence of an increase in risk of psychiatric referrals

in the first few weeks of minocycline exposure for women (IRR 2.82, 95% CI 0.96-8.27, p= 0.059).

Table 1. Demographic details of study population

		Exposed periods			*Unexposed periods*				
Patient group	**Number of patients with urgent psychiatric referral**	**Mean age at start exposure (Standard deviation [SD])**	**Duration (mean y) of follow-up during exposure (SD)**	**Number of outcomes during exposure**	**Duration (mean y) of follow-up before exposure (SD)**	**Number of outcomes before exposure**	**Mean age start post-exposure period (SD)**	**Duration (mean y) of follow-up after exposure (SD)**	**Number of outcomes after exposure**
All	167	17.47 (2.67)	0.27 (0.26)	14	1.25 (4.30)	22	17.99 (2.85)	3.78 (5.64)	131
Female	77	17.96 (3.28)	0.29 (0.31)	9	1.27 (4.45)	11	18.46 (3.40)	3.53 (5.25)	57
Male	90	17.05 (1.94)	0.26 (0.21)	5	1.23 (4.20)	11	17.58 (2.19)	3.98 (5.95)	74

Table 2. Case-series analysis for minocycline: association between exposure to minocycline and urgent psychiatric referral.

Outcome (total number)	Exposure	Patient years	Number of referrals	Crude Incidence Rate Ratio (RR)	Age adjusted IRR (95% confidence interval)	**P-value**
Psychiatric referrals (n=167)	Unexposed	2001.77	153	Baseline	Baseline	
	Exposed: Day 1-42	38.15	6	1.48 (0.64-3.43)	1.96 (0.82-4.71)	0.132
	Exposed: >42	47.85	8	1.54 (0.71-3.35)	1.97 (0.86-4.47)	0.107
	Post-exposure period	36.12	0	-	-	
Men (n=90)	Unexposed	1116.52	85	Baseline	Baseline	
	Exposed: Day 1-42	21.48	2	0.83 (0.20-3.50)	1.15 (0.26-5.15)	0.852
	Exposed: >42 days	25.26	3	1.08 (0.32-3.70)	1.47 (0.39-5.48)	0.569
	Post-exposure period	19.71	0	-	-	
Women (n=77)	Unexposed	885.26	68	Baseline	Baseline	
	Exposed: Day 1-42	16.67	4	2.36 (0.84-6.66)	2.82 (0.96-8.27)	0.059
	Exposed: >42 days	22.59	5	2.08 (0.75-5.79)	2.39 (0.83-6.92)	0.108
	Post-exposure period	16.41	0	-	-	

Sensitivity analyses:

When all unexposed cases who had been referred to psychiatric services were included in the self-controlled case series analysis to improve the correction for age, results were very similar to those seen in the primary analysis: IRR 1st 6 weeks 1.78, 95% CI 0.78-4.08, p=0.173; IRR remaining exposed time 1.79, 95% CI 0.85-3.77, p=0.127. 411 extra unexposed cases contributed to 4684.69 unexposed patient years.

With respect to people experiencing psychotic symptoms, within the group of 121 individuals, 33 were excluded as they were exposed to doxycycline/isotretinoin (n=8). Of the remaining 88 individuals, 63 were men (72%). Twenty-five percent of all individuals experienced hallucinations. Most events took place in periods of non-exposure to minocycline (n=81, IR = 808.5 per 10,000 py). Two individuals experienced an acute psychotic event during the first 6 weeks of exposure to minocycline (IR = 765.48 per 10,000 py). Two more individuals experienced an acute psychotic event in the remaining period of exposure to minocycline (IR = 766.45 per 10,000 py). Three events took place in the 2-month post-exposure period (IR = 1319.86 per 10,000 py). The age-adjusted IRR for the first 6 weeks of exposure was 0.85 (95% CI 0.20-3.64, p= 0.829). The age-adjusted IRR for the remaining exposure period was 0.92 (95% CI 0.21-4.05, p= 0.913) and 1.43 (95% CI 0.43-4.78, p= 0.559) in the post-exposure period. The small numbers did not allow for an analysis stratified by gender.

When the group of minocycline users and doxycycline users were combined, 377 individuals met the inclusion criteria, of whom 213 were female. Most events took place in periods of non-exposure (n=351, IR = 721.97 per 10,000 py). Ten individuals received an urgent psychiatric referral during the first six weeks of exposure (IR = 1176.22 per 10,000 py); nine

individuals in the remaining exposed period (IR = 1053.44 per 10,000 py); and 2 in the post-exposure period. The age-adjusted IRR for the first 6 weeks of exposure was 1.62 (95% CI 0.84-3.13, p= 0.147). The age-adjusted IRR for the remaining exposure period was 1.3 (95% CI 0.62-2.72, p= 0.485) and 0.41 (95% CI 0.10-1.68, p= 0.217) for the post-exposure period. The IRRs were similar for both men and women (1st 6 weeks of exposure IRR 1.60, 95% CI 0.56-4.57 vs IRR 1.68, 95% CI 0.73-3.89, respectively). The results for the analysis in which 42 doxycycline users were not excluded from the main analysis were as follows: IRR 1st 6 weeks of minocycline exposure 1.84 (95% CI 0.83-4.09, p==0.136).

No increased risk of urgent psychiatric referrals in the first few days of minocycline exposure was found when the first two days after receipt of a prescription for minocycline and the remaining exposure period were compared (IRR 1st two days 5.11, 95% CI 0.7-37.41, p=0.108). The results for the remaining time of the initial exposure period were similar to those found in the main analysis: IRR remaining 1st 6 weeks of exposure 1.75, 95% CI 0.68-4.49, p=0.248.

When *all* psychiatric referrals were used as an outcome measure, rather than *urgent* referrals, there was an increased risk during the first 42 days of minocycline exposure (IRR 1.76, 95% CI 1.39-2.22, p=0.001). Strong evidence of an increased risk was found when data for the first two days after receipt of a prescription were excluded from the data for remaining exposed time (IRR 1st 2 days of exposure: 5.93, 95% CI 3.74-9.39, p=0.000; IRR remaining 1st 6 weeks: 1.46, 95% CI 1.12-1.89, p= 0.005).

DISCUSSION

Main findings

There was no evidence found to support an association between receipt of a prescription for minocycline and risk of urgent psychiatric referral. Our study was conducted to further contribute to literature investigating the relationship between the use of minocycline, its anti-inflammatory properties, and neuro-inflammation in the pathophysiology of severe mental illness (Kelly et al., 2015). Our observational self-controlled case series study is the first to investigate a potential association between minocycline use in individuals diagnosed with acne and urgent psychiatric events using routinely collected health care data. This study was intended to measure any beneficial effect of treatment with minocycline on incident psychiatric referrals. Our data suggest that the taking of minocycline has no protective effect on the emergence of any mental health conditions.

Findings from sensitivity analyses

In the model used for both the main and sensitivity analyses we controlled for age in yearly bands. We believe the age adjustment was necessary as the crude models did not account for the increase in risk of psychiatric disease with age. The average peak incidence of psychiatric referrals in this study was 23 years. Unexposed cases were included in a first sensitivity analysis to improve the correction for age. The findings of the analysis with better adjustments for age were very similar to the results reported in the main analysis suggesting that the main analysis provided sufficient control for age.

In a second sensitivity analysis we measured the, until now, unknown association between receipt of minocycline and recording of psychotic symptoms. Our results suggest that receipt of a prescription for minocycline does not protect against psychotic symptoms.

The choice to exclude users of doxycycline from the study population in our main analysis was driven by concerns about attributing any protective effect of doxycycline to minocyline. When the exposure of interest was changed to include both users of minocycline and doxycycline our sample size more than doubled. Despite the resultant increase in power, the results remained the same.

We were aware that the first few days of minocycline prescribing may be expected to have a slightly higher rate of identification of all disorders, including severe mental illness. This is likely to be a spurious association created by GP attendance. It was deemed important, therefore, to separate the first two days after receipt of a prescription for minocycline from the remaining exposed time. Some evidence of an increased risk of urgent psychiatric referrals in the first two days of minocycline exposure was found, but this peak in diagnoses did not affect the overall results.

As data rating the urgency of referral were not entered for most individuals a sensitivity analysis was conducted in which *all* referrals rather than *urgen*t referrals were used as the outcome measure. As expected, this analysis allowed for greater sensitivity, but encompassed a wide array of non-specific reasons for referral. The two most common medical terms in the psychiatric referral file were “Psychiatric referral” and “Referral for further care”, followed by depressive disorder and behaviour disorder. The strong evidence for the increase in referral risk after receipt of a prescription for minocycline might be real, but could reflect the process by which referrals for latent psychiatric or psychological

symptoms, potentially due to the experience of severe acne, are made during periods of contact with the GPs for acne treatment.

Comparison with literature

Small RCTs have focussed on the role of minocycline as an adjunctive therapy in the treatment of schizophrenia. Kelly *et al*. (2015) reported no significant change in Brief Psychiatric Rating Scale psychosis factor and total score in a group of 52 patients using clozapine who received 200mg of minocycline or placebo as a daily add-on treatment for 10 weeks. Similarly, Levkovitz *et al.* (2008) found no evidence of a 6-month treatment effect of minocycline compared to placebo using the Scale for the Assessment of Negative Symptoms. By contrast, Chaudhry *et al*. (2012) reported some effects of minocycline added to treatment-as-usual in patients diagnosed with early schizophrenia measured using the Positive and Negative Syndrome Scale before and after 12 months of treatment.

The results of these RCTs and our study results are not directly comparable as we did not investigate the treatment effect of minocycline, nor did we restrict the study sample to patients with severe mental illness. Differences in results could be explained by duration of treatment. Most patients in the current study received minocycline for an average duration of 14 weeks. Effects may only be seen for longer usage periods.

Strengths and limitations

A strength of our study is the use of routinely collected healthcare data which are demographically and geographically representative of the UK population(Herrett et al., 2010; Garcia Rodriguez and Perez Gutthann, 1998). We chose a clinically meaningful outcome measure, recorded psychiatric referral, to indicate the suspicion of a severe mental condition.

Use of the self-controlled case series allowed for complete adjustment for non-time varying confounders, such as genetic susceptibility. The statistical power of the self-controlled case series can be equivalent to the power of a cohort study if exposure periods are short within a long observation period (Farrington, 2004). As antibiotic agents are usually prescribed in a transient fashion, the self-controlled case series was considered a powerful alternative design to a cohort study.

One of the study limitations is the small sample size. The current study was nested in a larger cohort study investigating the effect of minocycline on psychotic diagnoses later in life and was not originally set out to measure any instant protective effect of minocycline exposure. We restricted inclusion to individuals exposed to minocycline with an acne diagnosis. Our study lacked the power to investigate any protective effect of minocycline in a population previously diagnosed with mental illness. A larger study would have allowed us to stratify results, for instance by history of mental illness or by antipsychotic use. Despite these shortcomings, confidence intervals in our study excluded all but very small protective effects for minocycline there was no evidence of any antipsychotic effect for minocycline.

All comparisons in a self-controlled case series study are made within, rather than between, persons. This introduces a greater need to be precise when defining event times. Violating this particular assumption could lead to bias in a study when the timing of events is ill-defined. We acknowledge that psychiatric referrals could be made for long-standing symptoms, thereby compromising the self-controlled case series assumption that outcome measures are acute. Whilst CPRD data do not have a marker to measure acuity, we used GP coding of urgency, thereby making the assumption that urgent referrals at least reflected a clinical change from normal. In a sensitivity analysis we changed the outcome to first-time psychotic symptoms. Again, whilst acuity was not measured, it was the first time for all

individuals in our study sample to receive a diagnosis of psychotic symptoms and therefore likely to reflect an underlying change in health. To measure exposure, we used prescription data and, as with all studies using general practice prescription data, we were not able to confirm that medications were obtained or used as directed. We suspect the absolute increase in psychiatric referrals during minocycline use is indicative of care providers being consulted for multiple health complaints. Moreover, acne itself is associated with symptoms of depression(Lamberg, 1998). The possibility of reverse causality cannot be excluded as patients could have been prescribed minocycline as a direct result of symptoms related to their psychiatric referral.

Implications

Several studies have investigated the potential benefits of minocycline to treat positive and, more often, negative symptoms of schizophrenia. Whilst there may be potential for minocycline as an adjunctive therapy in treatment-resistant schizophrenia, we have found no evidence to support a protective effect of minocycline against psychiatric symptoms in adolescence. Further, larger scale, studies using routinely collected health care data to investigate the psychotropic or protective effect of minocycline in severe mental illness are recommended.

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